REMARKS

In view of the following remarks, the Examiner is requested to reconsider and allow Claims 1-2, 5-7, 10-11, 14-18, 24-30 and 32-40, the only claims pending and under examination in this application.

Formal Matters

Claims 1-2, 5-7, 10-11, 14-18, 24-30 and 32-40 were examined and rejected.

No claims are amended or cancelled.

Claim Rejection under 35 U.S.C. § 103

Claims 1-2, 5-7, 10-11, 14-18, 24-30 and 32-40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bockow (U.S. Patent No. 5,709,855) in view of Edwards (U.S. Patent No. 5,989,559), Herbert *et al.* (American J. of Industrial Medicine 37: 62-74, 2000), Hirano *et al.* (U.S. Patent No. 5,869,087), Liebschutz *et al.* (WO 02/22109) and the Applicants' specification.

In the response dated October 27, 2010, Applicants argued that the Examiner has not established a *prima facie* case of obviousness because: 1) the combined teaching of the cited references does not teach or suggest the amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed; and 2) one of ordinary skill in the art would not predict success in practicing the claimed method.

As will be discussed in greater detail below, Applicants submit that in maintaining the rejection: 1) the Examiner's assertion that the above claim element is inherent in the prior art method is insufficient to overcome Applicants' first argument; and 2) the Examiner has erred by discounting the substantial objective evidence and statements of record that one of ordinary skill in the art could not have predicted success in practicing the claimed method.

Examiner's assertion of inherency is insufficient to overcome Applicants' first argument

The combined teaching of the cited references fails to teach or suggest the amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed. Specifically, Applicants submit that Bockow does not disclose the application of a topical NSAID patch formulation for treatment of the symptoms of carpal tunnel syndrome, and nowhere does Edwards teach that application of the banana peel extract reduced symptoms of the individual for an **extended** period of time, i.e., 1 week or longer. Further, as Edwards provides no other data or teachings of treatment of carpal tunnel syndrome/median nerve pressure, Edwards fails to suggest that application of the banana peel extract would ameliorate any of these symptoms for a period of 1 week or longer.

As Herbert is cited solely for use of oral NSAIDs in treatment of carpal tunnel syndrome; Hirano and Liebschutz are cited for teaching diclofenac patches; and the instant specification is cited for teaching a commercially available hydrogel adhesive patch; these references do not remedy the deficiencies of Bockow and Edwards.

In attempting to refute the Applicants' first argument, summarized above, the Examiner acknowledges that the cited references are silent as to the amelioration of at least one symptom for a period of 1 week or longer, as claimed, but asserts that this claim element is merely an inherent benefit of the prior art method (i.e., the method of Bockow modified as proposed by the Examiner according to the combined teaching of the cited references). See Final Office Action, page 5.[1]

In this case, the Examiner asserts that the claim element of amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer is inherently present in the method disclosed in the prior art. However, Bockow

[1] "The fact that Applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method." Final Office Action, page 5, lines 17-19.

merely teaches a composition that optionally includes a NSAID for treating pain. The Examiner relies on Edwards for application to the palmar dermal surface of the host to treat CTS, and the combined teaching of Herbert, Hirano and Liebschutz to modify Bockow's method and allegedly render obvious the Applicants' claimed method.

As such, the Examiner compares the claimed method to an allegedly obvious **proposed modification to Bockow's method**, and asserts that the only difference is an undiscovered beneficial effect. However, that is not the correct standard for inherency set forth by the courts and is different from the facts presented in the cases employed by the Examiner to support the Examiner's position.

In support of the above assertion, the Examiner cites the following case law: *Bristol-Myers Squibb Company v Ben Venue Laboratories*[2], *In re Woodruff* [3] and *In re Baxter Travenol Labs.*[4] See Final Office Action, page 5.

In *Bristol-Myers Squibb Company v Ben Venue Laboratories* the claimed method directed to a three-hour paclitaxel administration was found invalid over a single anticipating reference by Kris[5] which reports that patients were treated with three-hour infusions of paclitaxel within the claimed dosage ranges but observed no antitumour response. The court determined that the claimed method was **inherently anticipated** because reducing toxicity and tumor regression were necessary consequences of practicing Kris' method.

Similarly, *In re Woodruff* concerns a claimed method for inhibiting growth of fungi on vegetables. The sole prior art reference McGill described a method of storing

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[2] Bristol-Myers Squibb Company v Ben Venue Laboratories, 58 USPQ2d 1508 (CAFC 2001), "it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure".

[3] *In re Woodruff*[3] 16 USPQ2d 1508 (CAFC 2001),"It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable."

[4] *In re Baxter Travenol Labs* 21 USPQ2d 1281 (Fed. Cir. 1991)

[5] Kris *et al.*, Phase I trial of Taxol given as a 3-hour infusion every 21 days, 70 Cancer treatment reports 605-607 (1986).

vegetables under atmospheric and temperature conditions that anticipated those of Woodruff. The Federal Circuit found that the two differences between the claimed invention and McGill: the slightly different ranges of atmospheric conditions and the new undiscovered benefit of the method did not render the claimed method patentable.

Finally, *In re Baxtor Travenol Labs* concerns a blood bag system containing an additive (DEHP) to improve the bag's red blood cell storage capability. The claims were held to be anticipated by the reference Becker which taught the same blood bag system using commercial blood bags that at the time were known to contain DEHP.

As such, in each of the above three cases,[2,4,5] a single anticipatory reference disclosed all the steps of the claimed method. The courts determined that when all the elements of a claimed invention are necessarily present in **a single prior art reference** then the claims are **inherently anticipated**.

In this case, the Examiner has erred by relying on an assertion of inherent undiscovered benefits, not in the closest prior art method, but rather in a proposed combination of prior art references that allegedly renders the claimed method obvious.

In Perricone v Medicis Pharm. Corp.,[6] the Federal Circuit found claims drawn to a method of topically *treating sunburn* using an ascorbic acid formulation to be valid over the disclosed prior art method of using an ascorbic acid formulation to *avoid sunburn*. The Federal Circuit found that the lower District Court failed to realize that there was an important distinction between the prior art method and the narrower claimed method, and that "unrealized possibilities do not alter the analysis in this case where Pereira [the prior art] does not disclose topical application to skin sunburn."

In the present case, it appears that the Examiner similarly fails to acknowledge the distinction between NSAID compositions of the cited prior art and the closest prior

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[6] Perricone v. Medicis Pharm. Corp. 432 F.3d 1368 (Fed. Cir. 2005)

art methods which do not disclose topical application of a NSAID composition to a palmar dermal surface proximal to the carpal tunnel, as claimed.

Furthermore, merely pointing to an allegedly obvious combination of Bockow, Edwards, Herbert, Hirano and Liebschutz and asserting that amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed, is inherent in this allegedly obvious combination because there is no reason to believe otherwise is insufficient to overcome Applicants' arguments and supporting evidence.

The Declaration of Dr. Larry Caldwell filed October 27, 2010, provides statements of one of ordinary skill in the art indicating that just because Edwards' extract cream may give immediate relief of symptoms does not mean that the cream would work over an extended period of time. As such, neither Bockow nor Edwards teaches or suggests amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness because the combined teaching of the cited references fails to teach or suggest the amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed.

<u>The Examiner has erred by discounting Applicants' substantial objective evidence</u>

Furthermore, in rebutting the Applicants' second argument that one of ordinary skill in the art could not have predicted success in practicing the claimed method, the Examiner has erred by discounting the substantial objective evidence and statements of record provided by the Applicants, as discussed in greater detail below.

Applicants have provided substantial objective evidence and statements of record (see Declaration of Dr. Larry Caldwell under 37 C.F.R. § 1.132 dated October

27, 2010, hereinafter "the Caldwell Declaration", and the Declaration of Mr. Galer dated November 21, 2006, hereinafter "the Galer Declaration") that support the contention one of ordinary skill in the art would not have predicted success in practicing the claimed invention prior to the Applicants' work reported in the present application.

Claim 1 recites, "a topical patch NSAID formulation **consisting of**: an adhesive matrix; **an NSAID dissolved in said adhesive matrix**; and a backing" (emphasis added). As such, the claimed method is directed to topical application of a formulation that includes a NSAID as the only active agent, to ameliorate at least one symptom associated with median nerve pressure for a period of 1 week or longer.

In attempting to provide a predicted success in practicing the claimed method, the Examiner points to Bockow and Edwards' combined teaching of topical compositions for treatment of CTS. Bockow is directed to a composition that includes an omega fatty acid and spirulina as essential ingredients where a NSAID is merely an optional ingredient. Edwards is directed to a banana peel extract that does not include a NSAID.

However, Bockow and Edwards both rely on compositions that do not include a NSAID as the only active agent and that have completely different types of activities to those of the claimed invention. For example, Bockow teaches that the activity of his composition is based on the synergistic combination of the essential omega fatty acid and spirulina ingredients, rather than a NSAID. See e.g., Bockow, column 3, lines 14-15. The activity of Edwards' composition is based on compounds with completely different structures and mechanisms of action (see discussion below).

Further, the deficiencies of Bockow and Edwards are not remedied by the remaining cited references because:

Herbert is directed solely to oral NSAIDs that do not predict success for transdermal NSAIDs;

Liebschutz and Hirano merely teach an NSAID patch formulation but provide no teachings or data to support a predicted success for amelioration of at least one symptom associated with median nerve pressure; and

the Applicants' specification is cited solely for disclosing a hydrogel.

As such, the activities of the compositions relied on by the Examiner have not been equated with the activity of NSAIDs, and are not sufficient to provide a predicted success in practicing the claimed method of topically applying a composition that includes a NSAID as the only active agent to ameliorate at least one symptom associated with median nerve pressure, as claimed.

In the previous response of October 27, 2010, Applicants showed that Edwards fails to support a predicted success in practicing the claimed method because Edwards's active agents have structures that are distinct from NSAID drugs and act via a completely different mechanism of action. Applicants provided supporting objective evidence and statements of one of ordinary skill in the art in the Caldwell Declaration, (see points 4a and 4b, pages 3-5).

In the Final Office Action, the Examiner provides no evidence to rebut Applicants' supporting evidence and statements regarding Edwards' extract. Instead the Examiner asserts that Edwards is merely a secondary reference to show topical application of any medication on or near the sites of pain. See Office Action, pages 6 to 7, bridging paragraph.

As such, by dismissing the substantial objective evidence and statements regarding Edwards, the Examiner appears to concede that topical application of Edwards' unrelated extract does not predict success for the claimed method. In attempting to provide a predicted success, the Examiner instead turns to Bockow and Herbert. See Office Action, page 7, lines 7-10.

However, Bockow fails to support a reasonable expectation of success in practicing the claimed method because:

1) the activity of Bockow's formulation is based on the synergistic combination of an omega fatty acid and spirulina combination that has not been equated with the activity of an NSAID as the only active agent; and

2) Bockow provides no working exemplification of treatment of CTS with a NSAID formulation – in particular, amelioration of at least one symptom associated with pressure applied to the median nerve of the carpal tunnel of a host for a period of 1 week or longer following application.

As supported by the Caldwell Declaration, prior to the reduction to practice reported in the current application, there was no reasonable expectation of success that application of a NSAID topical formulation could be used to treat carpal tunnel syndrome/median nerve pressure. The Applicants are aware of no report prior to the priority date of the current application of the use of such a topical formulation to treat carpal tunnel syndrome. See the Caldwell Declaration, item 5.

In addition, Herbert merely discloses that oral NSAIDs, local steroidal drug injections, iontophoresis and ultrasound may be effective treatments for CTS. Nowhere does Herbert teach or suggest that application of a transdermal patch would be an effective treatment for CTS. Herbert's suggestion of oral NSAID treatment of CTS does not provide support for a predicted success in practicing the claimed method because "it is well known in the art that just because an active agent is administered orally to treat a medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition." See statement 6a and supporting references of the Galer Declaration filed November 21, 2006.

For example, Exhibit A of the Galer Declaration (Moore *et al.*, Br. J. Clin. Pharmacol. (1994) 37:227-30) reports that topical application of morphine had no significant effect when compared with placebo for the treatment of pain in contrast to

oral administration of morphine that is known to be effective in treating post-operative pain. For example, Lynch *et al.* (Anesthesiology (2005) 103:140-6, Exhibit A of the Galer Declaration) reports that use of a topical 2% amitriptyline formulation in treating patients with neuropathic pain had no significant effect when compared with placebo, in contrast to oral administration of amitriptyline which is known to be effective. These references demonstrate that just because an active agent is administered orally to treat a given medical condition does not predict that the active agent can be effective when administered topically.

In the Final Office Action, the Examiner provides no evidence or reasoning to rebut the substantial objective evidence of record that Herbert's teaching of oral NSAID treatment does not predict success for topical NSAID formulations.

The Examiner dismisses the Applicants' substantial objective evidence and statements of record, summarized above, by merely asserting that, "HERBERT reference teaches that it is commonly known in the art to use NSAID to treat carpal tunnel syndrome. Thus, one skilled in the art would have more than reasonable expectation of success." See Final Office Action, page 7, lines 7-10.

Furthermore, neither Hirano nor Liebschutz provide a working exemplification of transdermal delivery in a host for treatment of any condition, much less treatment of any symptoms of CTS/median nerve pressure. Hirano and Liebschutz merely provide examples showing some *in vitro* permeation of hairless mouse skin or guinea pig skin. However, *In vitro* permeation through isolated mouse skin does not necessarily translate to transdermal delivery in a host[7] much less to amelioration of at a symptom

[7] K. Walters, "Dermatological and transdermal formulations," in Drugs and the pharmaceutical sciences, Vol. 119, Marcel Dekker, New York, 2002, page 241, paragraphs 2 and 4.
"It is important to consider the ability of in vitro skin penetration techniques to predict skin permeation in vivo. Unless it can be demonstrated that in vitro skin penetration data is reasonable similar to absorption across skin in situ, there is little value in obtaining this data."
"Many such studies have been performed using small laboratory animals, and their relevance to human skin has always been questionable, especially in terms of risk assessment."

associated with median nerve pressure for a period of 1 week or longer. As discussed above, one would not predict success without actually performing experiments and obtaining positive results.

Thus, in contrast to the Examiner, the Applicants have provided substantial objective evidence including a multitude of scientific publications and Declarations under 1.132 by those of ordinary skill in the art supporting that one of ordinary skill in the art could not have predicted success that topical application of a NSAID would ameliorate at least one symptom associated with median nerve pressure for a period of 1 week or longer. The Examiner has erred by dismissing the Applicants' substantial objective evidence and supporting statements.

In sum, in attempting to rebut Applicants' arguments against a *prima facie* case of obviousness: 1) the Examiner's assertion that amelioration of at least one symptom associated with median nerve pressure for a period of a week or longer is inherent in the prior art method is insufficient; and 2) the Examiner has erred by discounting the substantial objective evidence and statements of record that one of ordinary skill in the art could not have predicted success in practicing the claimed method.

In view of the above, the claims are not rendered obvious under 35 U.S.C. § 103(a) over the cited references. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 24-33

The Applicants submit that Claims 24-33 are further distinguished over the combined teaching of the cited references for specifying a hydrogel patch.

In maintaining this rejection over Claims 24-33, the Examiner cites Bockow, Edwards and Herbert for disclosing NSAID formulations for treating CTS. The Examiner relies on Hirano and Liebschutz for disclosing transdermal diclofenac patches.

However, nowhere do the cited references disclose a hydrogel patch formulation, as claimed.

In modifying the patches of the prior art methods to arrive at the claim element of a hydrogel patch, the Examiner relies solely on the Applicants' disclosure of "Neurodol Tissugel" as a marketed product at page 9, lines 21-23 of the present specification, and asserts that "it would have been obvious to purchase and use a commercially available patch [ ], because it would be easier than making from scratch." See Office Action dated May 27, 2010, page 7, lines 7-9.

"In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958)". See MPEP § 2144.06.

Applicants submit that the Examiner has provided no teachings of the cited references that support substituting a hydrogel patch into the compositions of the prior art methods. Merely pointing to Applicants' disclosure of "Neurodol Tissugel" as a marketed product does not show equivalency of a hydrogel patch or provide a reason to modify the prior art compositions, as proposed by the Examiner.

Thus, the Examiner has failed to establish a prima facie case of obviousness. Accordingly, withdrawal of this rejection of Claims 24-33 is respectfully requested.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CALD-005.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: February 18, 2011 By: /Glenn J. Foulds, Reg. No. 64,714/
Glenn J. Foulds
Registration No. 64,714

Date: February 18, 2011 By: /Bret E. Field, Reg. No. 37,620/
Bret E. Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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